Melaleuca, Inc.

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Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W.
Washington, DC 20204

Re: Section 403(r)(6) Notification

Dear Sir or Madam:

In accordance with the requirements of section 403(r)(6) of the Federal Food, Drug and Cosmetic Act, Melaleuca, Inc., notifies FDA that it has begun using the following statement:

> And based on preliminary human data, we have found that our product may have a substantial effect on cardiovascular health.
>
> In preliminary studies, PROVEXCV reduced *in vitro* LDL cholesterol oxidation at over two times the level of vitamin E. In addition, preliminary *ex vivo* tests showed that PROVEXCV inhibited platelet activity (when stimulated with collagen) at over 50%.
>
> PROVEXCV is a natural dietary supplement that has shown to be a powerful *in vitro* antioxidant and a strong *ex vivo* platelet-inhibitor with the potential to offer more health-enhancing benefits tot eh heart than other known natural products.
>
> Flavonoids are natural compounds found in fruits, vegetables, red wine, some fruit juices, and tea that have been tested and found to have potential health benefits to humans.
>
> While the dietary intake of flavonoids, in general, has been shown to have a number of health benefits, PROVEXCV has been uniquely formulated and evaluated for its potential effects on the cardiovascular system. Specifically, it has been and will continue to be studied for its ability to inhibit LDL cholesterol oxidation and to turn down platelet activity. In addition, studies are underway

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to determine its potential to provide positive stimulus to the endothelial lining of arteries.

PROVEXCV has shown, in a series of *in vitro* tests with human LDL cholesterol, to be more than twice as potent an antioxidant as compared to equivalent amounts of vitamin E.

Research has found that certain flavonoids can help regulate platelet activity, thus helping to maintain normal circulation.

Whole blood platelet aggregation studies were performed on 14 humans before and after seven days of daily consumption of PROVEXCV. In each of the blood samples, blood platelets were stimulated by four different substances: collagen, adenosine diphosphate (ADP), ADP combined with epinephrine, and phorbol 12-myristate 13-acetate (PMA). The platelet aggregation response to:

Collagen--decreased by $52 \pm 31\%$ ($p < 0.005$)
ADP--decreased by $42 \pm 37\%$ ($p < 0.008$)
ADP and epinephrine--decreased by $28 \pm 7\%$ ($p < 0.02$)
PMA--decreased by $29 \pm 9\%$ ($p < 0.01$)

after daily consumption of PROVEXCV

In seven human subjects, PROVEXCV was taken orally for 14 days . . . Ex vivo whole platelet activity (PA) studies . . . showed collagen PA was decreased by $44 \pm 9\%$ and the synergism between collagen-and epinephrine-induced PA was inhibited by $32 \pm 11\%$.

Recent studies have shown that grape juice can stimulate the endothelial lining of arteries to help maintain normal vasodilation. Since PROVEXCV has similar components to grape juice (through its grape skin and seed extracts), studies are underway to determine its potential in supporting normal vasodilation.

Several scientists have studies flavonoids and their benefits to the cardiovascular system.

In addition, the potential of PROVEXCV to help maintain proper vasodilation, the effects of combining it with other platelet-inhibiting products, and its other possible benefits are being further investigated and explored.

Melaleuca has made a commitment to continue to add to the scientific evidence necessary to further solidify this product's significant benefits to the

cardiovascular system.

However, unlike similar flavonoid supplements, PROVEXCV has shown to inhibit platelet activity and to reduce LDL cholesterol oxidation through preliminary *in vitro, in vivo* animal, and *ex vivo* human scientific studies.

Flavonoids are compounds naturally found in fruits, vegetables, red wine, grape juice, and tea that have been found to have many health benefits. One particular type of plant flavonoid found in grape seeds is the proanthocyanidin, which is known to provide powerful antioxidant protection to help control LDL cholesterol oxidation. In fact, in a standard *in vitro* study, certain proanthocyanadins proved to be 10 times more powerful than vitamin E in one area of antioxidant activity. In addition, proanthocyanadins strengthen connective tissues in the body and fortify capillary wall structure, leading to improved circulation. They have also demonstrated a platelet-inhibiting action. Grape seed extract is a leading source of proanthocyanadins. This extract also contains gallic esters, which are very powerful free-radical scavengers.

Grape seed: *In vivo* animal and *ex vivo* human studies show: flavonoids in grape seed regulate platelet activity; Contains gallic esters, the most active scavengers of free radicals.

Flavonoids found in the skin of grapes may contain many of the common components of grape juice, such as anthocyanins (another class of flavonoids), tartaric acid, tannins, sugars, minerals, etc. These components are thought to contribute to grape skin's antiplatelet properties. In addition, the anthocyanins possess free-radical-scavenging action that protect against LDL cholesterol oxidation.

Grape skin: A leading source of anthocyanins, another group of beneficial flavonoids that contribute to inhibiting platelet activity.

These flavonoids [ginkgo biloba] assist the blood vessels in contracting and dilating at the proper times and levels to allow the blood to flow efficiently. In addition, studies have shown that ginkgo possesses antioxidant properties that help to control LDL cholesterol oxidation and antiplatelet properties that help regulate blood platelet activity.

Ginkgo biloba: The leaves contain flavonoids that help regulate blood flow through arteries and other blood vessels.

Bilberry: Its anthocyanosides have demonstrated the ability to prevent free-

radical damage. These flavonoids also help to maintain the integrity of capillaries and to stabilize collagen, which in turn helps to give the walls of the arteries their structural integrity. Studies show that bilberry also inhibits platelet activity.

Quercitin is an individual flavonoid commonly found in grapes and other fruits as well as in hops, malt, barley, and other plants. Researchers used this flavonoid in studies and found that, all by itself, quercitin significantly inhibits platelet activity. It has also demonstrated the ability to scavenge free radicals and to reduce the oxidation of LDL cholesterol.

Quercitin: Has powerful platelet-regulating and free-radical-scavenging properties.

These statements contain the statutory disclaimer. The name of the dietary supplement is PROVEXCV™, and the relevant dietary ingredients are grape seed extract, ginkgo biloba extract, bilberry extract, grape skin extract, quercitin powder, and fungal and plant proteases.

I certify that the foregoing is complete and accurate, and that Melaleuca, Inc., has substantiation that the statements are truthful and not misleading.

Very truly yours,

Melaleuca, Inc.

McKay Christensen

McKay Christensen
Chief Operating Officer

HC/ds